Inferring Biological Regulatory Networks from Process Hitting models

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Joint work with:
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MeForBio team: Algebraic modeling to study complex dynamical biological systems
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1) Two main models
   - Historical model: Biological Regulatory Network (René Thomas)
   - New developed model: Process Hitting

2) Allow efficient translation from Process Hitting to BRN
**The Process Hitting modeling**

[PMR12-MSCS]

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**Sorts:** components  \( a, b, z \)
Sorts: components $a, b, z$

Processes: local states / levels of expression $z_0, z_1, z_2$
Inferring BRNs from PH models o Frameworks Definitions o The Process Hitting

The Process Hitting modeling
[PMR12-MSCS]

Sorts: components  \( a, b, z \)
Processes: local states / levels of expression  \( z_0, z_1, z_2 \)
States: sets of active processes  \( \langle a_0, b_1, z_0 \rangle \)
The Process Hitting modeling

[PMR12-MSCS]

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**Actions:** dynamics \( b_1 \rightarrow z_0 \overrightarrow{z_1}, a_0 \rightarrow a_0 \overrightarrow{a_1}, a_1 \rightarrow z_1 \overrightarrow{z_2} \)
**The Process Hitting modeling**

\[\text{[PMR12-MSCS]}\]

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Inferring BRNs from PH models

Frameworks Definitions

The Process Hitting modeling

[PMR12-MSCS]

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Actions: dynamics \( b_1 \rightarrow z_0 \uparrow z_1, a_0 \rightarrow a_0 \uparrow a_1, a_1 \rightarrow z_1 \uparrow z_2 \)
Adding cooperations

[PMR12-MSCS]

How to introduce some cooperation between sorts? \[ a_1 \wedge b_0 \rightarrow z_1 \uparrow z_2 \]
Adding cooperations

How to introduce some cooperation between sorts? \[ a_1 \land b_0 \rightarrow z_1 \rightarrow z_2 \]
Adding cooperations

[PMR12-MSCS]

How to introduce some *cooperation* between sorts? \( a_1 \land b_0 \rightarrow z_1 \uparrow z_2 \)
Adding cooperations

[PMR12-MSCS]

How to introduce some cooperation between sorts?

Solution: a cooperative sort \( ab \)

\[
\begin{align*}
\text{a} & \quad \text{b} \\
1 & \quad 1 \\
0 & \quad 0 \\
\end{align*}
\]

\[
\begin{align*}
\text{ab} \\
11 & \\
10 & \\
01 & \\
00 & \\
\end{align*}
\]

\[
\begin{align*}
\text{z} \\
2 \\
1 \\
0 \\
\end{align*}
\]
How to introduce some **cooperation** between sorts? \[ a_1 \land b_0 \rightarrow z_1 \uparrow z_2 \]

Solution: a **cooperative sort** \( ab \)
Adding cooperations

[PMR12-MSCS]

How to introduce some cooperation between sorts? $a_1 \land b_0 \rightarrow z_1 \uparrow z_2$

Solution: a cooperative sort $ab$
How to introduce some cooperation between sorts?

Solution: a cooperative sort \( ab \)
Adding cooperations

How to introduce some **cooperation** between sorts?  \( a_1 \land b_0 \rightarrow z_1 \uparrow z_2 \)

Solution: a **cooperative sort** \( ab \)

Constraint: each configuration is represented by one process \( \langle a_1, b_0 \rangle \)
Adding cooperations

[PMR12-MSCS]

How to introduce some **cooperation** between sorts? \( a_1 \land b_0 \rightarrow z_1 \uparrow z_2 \)

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Solution: a cooperative sort \( ab \)

Constraint: each configuration is represented by one process \( \langle a_1, b_0 \rangle \Rightarrow ab_{10} \)
Adding cooperations

[PMR12-MSCS]

How to introduce some **cooperation** between sorts? \[ a_1 \land b_0 \rightarrow z_1 \uparrow z_2 \]

Solution: a **cooperative sort** \( ab \) to express \( a_1 \land b_0 \)

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How to introduce some *cooperation* between sorts? \( a_1 \land b_0 \to z_1 \uparrow z_2 \)

Solution: a *cooperative sort* \( ab \) to express \( a_1 \land b_0 \)

Constraint: each configuration is represented by one process \( \langle a_1, b_0 \rangle \Rightarrow ab_{10} \)

Advantage: regular sort; drawbacks: complexity, temporal shift
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context

\[ \langle a_1, \{ b_0, b_1 \}, c_0, z_0 \rangle \]
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \( \langle a_1, \{b_0, b_1\}, c_0, z_0 \rangle \)

- Objectives
  \[ \overset{\rightarrow}{d_1} \overset{\leftarrow}{b_1} \overset{\rightarrow}{d_2} \]
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \[
  \langle a_1, \{b_0, b_1\}, c_0, z_0 \rangle
  \]

- Objectives
  \[
  \left[ \overset{\dagger}{d_1} :: \overset{\dagger}{b_1} :: \overset{\dagger}{d_2} \right]
  \left[ \overset{\dagger}{d_2} \right]
  \]
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \[ \langle a_1, \{ b_0, b_1 \}, c_0, z_0 \rangle \]

- Objectives
  \[ [ \uparrow d_1 :: \uparrow b_1 :: \uparrow d_2 ] \]
  \[ [ \uparrow d_2 ] \]

→ Concretization of the objective = scenario

\[ a_0 \rightarrow c_0 \uparrow c_1 :: b_0 \rightarrow d_0 \uparrow d_1 :: c_1 \rightarrow b_0 \uparrow b_1 :: b_1 \rightarrow d_1 \uparrow d_2 \]
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \[ \langle a_1, \{ b_0, b_1 \}, c_0, z_0 \rangle \]

- Objectives
  \[ \overset{\rightharpoonup}{d_1} \:: \overset{\rightharpoonup}{b_1} \:: \overset{\rightharpoonup}{d_2} \]
  \[ \overset{\rightharpoonup}{d_2} \]

→ Concretization of the objective = scenario

\[ a_0 \rightarrow c_0 \overset{\rightharpoonup}{c_1} :: \] \( b_0 \rightarrow d_0 \overset{\rightharpoonup}{d_1} :: \] \( c_1 \rightarrow b_0 \overset{\rightharpoonup}{b_1} :: \) \( b_1 \rightarrow d_1 \overset{\rightharpoonup}{d_2} \]
Static analysis: successive reachability

Successive reachability of processes:

• Initial context
\[ \langle a_1, \{b_0, b_1\}, c_0, z_0 \rangle \]

• Objectives
\[ [ \overset{\cdot}{d_1} \cdot \overset{\cdot}{b_1} \cdot \overset{\cdot}{d_2} ] \]

\[ [ \overset{\cdot}{d_2} ] \]

→ Concretization of the objective = scenario
\[ a_0 \rightarrow c_0 \overset{\cdot}{c_1} \cdot b_0 \rightarrow d_0 \overset{\cdot}{d_1} \cdot c_1 \rightarrow b_0 \overset{\cdot}{b_1} \cdot b_1 \rightarrow d_1 \overset{\cdot}{d_2} \]
Inferring BRNs from PH models  ○  Frameworks Definitions  ○  The Process Hitting

Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \[ \langle a_1, \{ b_0, b_1 \}, c_0, z_0 \rangle \]

- Objectives
  \[ [ \Rightarrow d_1 :: \Rightarrow b_1 :: \Rightarrow d_2 ] \]
  \[ [ \Rightarrow d_2 ] \]

→ Concretization of the objective = scenario
  \[ a_0 \rightarrow c_0 \Rightarrow c_1 :: b_0 \rightarrow d_0 \Rightarrow d_1 :: c_1 \rightarrow b_0 \Rightarrow b_1 :: b_1 \rightarrow d_1 \Rightarrow d_2 \]
Static analysis: successive reachability

[PMR12-MSCS]

Successive reachability of processes:

- Initial context
  \[ \langle a_1, \{b_0, b_1\}, c_0, z_0 \rangle \]

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  \[
  \begin{align*}
    & \vdash d_1 :: \vdash b_1 :: \vdash d_2 \\
    & \vdash d_2
  \end{align*}
  \]

→ Concretization of the objective = scenario
  \[
  a_0 \rightarrow c_0 \vdash c_1 :: b_0 \rightarrow d_0 \vdash d_1 :: c_1 \rightarrow b_0 \vdash b_1 :: b_1 \rightarrow d_1 \vdash d_2
  \]
Static analysis by abstractions:

→ Directly checking an objective sequence $R$ is hard

→ Rather check the approximations $P$ and $Q$, where $P \Rightarrow R \Rightarrow Q$:
Over- and Under-approximations

[PMR12-MSCS]

Static analysis by abstractions:

→ Directly checking an objective sequence \( R \) is hard
→ Rather check the approximations \( P \) and \( Q \), where \( P \Rightarrow R \Rightarrow Q \):

![Diagram showing over-approximation and exact solution]
Static analysis by abstractions:

→ Directly checking an objective sequence $R$ is hard
→ Rather check the approximations $P$ and $Q$, where $P \Rightarrow R \Rightarrow Q$: 

Over-Approximation

Exact solution

$R$

$\neg Q$
Over- and Under-approximations
[PMR12-MSCS]

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[PMR12-MSCS]

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[Diagram showing Over- and Under-approximations]
Inferring BRNs from PH models

Frameworks Definitions

The Process Hitting

Over- and Under-approximations

[PMR12-MSCS]

Static analysis by abstractions:

→ Directly checking an objective sequence $R$ is hard
→ Rather check the approximations $P$ and $Q$, where $P \Rightarrow R \Rightarrow Q$:

Linear w.r.t. the number of sorts and exponential w.r.t. the number of processes in each sort
→ Efficient for big models with few levels of expression
The Process Hitting modeling

- **Dynamic** modeling with an **atomistic** point of view
  - Independent actions
  - Cooperation modeled with cooperative sorts

- **Efficient static analysis**
  - Reachability of a process can be computed in **linear time** in the number of sorts

- Useful for the study of **large biological models**
  - Up to hundreds of sorts

- (Future) extensions
  - Actions with stochasticity
  - Actions with priorities
  - Continuous time with clocks?
Inferring BRNs from PH models ○ Frameworks Definitions ○ Thomas’ Modeling

Biological Regulatory Network (Thomas' modeling) [RCB08]

Proposed by René Thomas in 1973, several extensions since then

Historical bio-informatics model for studying genes interactions
Widely used and well-adapted to represent dynamic gene systems
Biological Regulatory Network (Thomas' modeling)

Interaction Graph: structure of the system (genes & interactions)
**Biological Regulatory Network (Thomas' modeling)**

![Interaction Graph]

**Interaction Graph**: structure of the system (genes & interactions)

**Nodes**: genes

- **Name**: $a, b, z$
- **Possible values (levels of expression)**: $0..1, 0..2$

**Table**

<table>
<thead>
<tr>
<th>$a$</th>
<th>$b$</th>
<th>$k_{z,ω}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-$</td>
<td>$+$</td>
<td>1</td>
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<tr>
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[RCB08]
Inferring BRNs from PH models o Frameworks Definitions o Thomas’ Modeling

Biological Regulatory Network (Thomas’ modeling) [RCB08]

Interaction Graph: structure of the system (genes & interactions)

Nodes: genes
   → Name   \( a, b, z \)
   → Possible values (levels of expression) 0..1, 0..2

Edges: interactions
   → Threshold 1
   → Type (activation or inhibition) + / −
Biological Regulatory Network (Thomas’ modeling)

Parametrization: strength of the influences (cooperations)

Maps of tendencies for each gene

→ To any influences of predecessors \( \omega \)

→ Corresponds a parameter \( k_{x,\omega} \)
Biological Regulatory Network (Thomas’ modeling)  

\[ [RCB08] \]

**Parametrization**: strength of the influences (cooperations)

Maps of tendencies for each gene

- To any *influences of predecessors* \( \omega \)
- Corresponds a parameter \( k_{x,\omega} \)

“\( k_{z,\{a^+,b^+\}} = 2 \)” means: “\( z \) tends to 2 when \( a \geq 1 \) and \( b < 1 \)”
Biological Regulatory Network (Thomas’ modeling)

[RCB08]

- **Frameworks Definitions**
  - Thomas’ Modeling

- **Biological Regulatory Network**
  - All needed information to run the model or study its dynamics:
    - Build the State Graph
    - Find reachability properties, fixed points, attractors
    - Other properties...

- **Strengths**: well adapted for the study of biological systems

- **Drawbacks**: inherent complexity; needs the full specification of cooperations
Inferring a BRN with Thomas’ parameters

\[
\begin{array}{c|c}
\omega & k_{z,\omega} \\
\emptyset & 1 \\
\{b\} & 0 \\
\{a\} & 2 \\
\{a; b\} & 1 \\
\end{array}
\]
Inferring a BRN with Thomas’ parameters

\[
\begin{array}{c|c}
\omega & k_{z, \omega} \\
\emptyset & 1 \\
\{b\} & 0 \\
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Inferring a BRN with Thomas’ parameters

Maxime FOLCHETTE
Inferring BRNs from PH models

Translating a Process Hitting into a BRN

Interaction Graph Inference

Inferring the Interaction Graph

[CMSB12]

Exhaustive search in all possible configurations

1. Pick one regulator [a], and choose an active process for all the others [b].

2. Change the active process of this regulator [a_0, a_1] and watch the focal processes.

3. Conclude locally: (a_0 ↖ a_1 ⇒ z_0 ↖ z_2) ⇒ activation (+) & threshold = 1.

4. Iterate

Problematic cases:

→ No focal processes (cycle)

→ Opposite influences (+ & −)

⇒ Unsigned edge
Inferring the Interaction Graph

[CMSB12]

Exhaustive search in all possible configurations:

1. Pick one regulator \(a\), and choose an active process for all the others \(b\).
2. Change the active process of this regulator \(a\) and watch the focal processes.
3. Conclude locally: \(a_0 \leftrightarrow a_1 \Rightarrow z_0 \leftrightarrow z_2\) \(\Rightarrow\) activation (+) & threshold = 1.
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Problematic cases:
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\(\Rightarrow\) Unsigned edge
Inferring the Interaction Graph

Exhaustive search in all possible configurations
→ **Exhaustive search in all possible configurations**

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
Inferring the Interaction Graph

[CMSB12]

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Inferring BRNs from PH models

Translating a Process Hitting into a BRN

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Inferring BRNs from PH models ○ Translating a Process Hitting into a BRN ○ Interaction Graph Inference

Inferring the Interaction Graph

\[ \text{[CMSB12]} \]

\[ \{ b = 1 \} \quad \{ b = 0 \} \Rightarrow 1^+ \]

→ **Exhaustive search in all possible configurations**

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
2. Change the active process of this regulator \([a_0, a_1]\) and watch the **focal processes**.
3. Conclude locally: \( (a_0 \uparrow a_1 \Rightarrow z_0 \uparrow z_2) \Rightarrow \text{activation ( + ) & threshold } = 1 \).
4. Iterate
Inferring the Interaction Graph

Inferring BRNs from PH models ○ Translating a Process Hitting into a BRN ○ Interaction Graph Inference

→ Exhaustive search in all possible configurations

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
2. Change the active process of this regulator \([a_0, a_1]\) and watch the focal processes.
3. Conclude locally: \((a_0 ↗ a_1 ⇒ z_0 ↗ z_2) ⇒ \text{activation (+) & threshold } = 1\).
4. Iterate

\[\{b = 1\} \quad \{b = 0\} ⇒ 1+\]
Inferring the Interaction Graph

[CMSB12]

→ Exhaustive search in all possible configurations

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
2. Change the active process of this regulator \([a_0, a_1]\) and watch the focal processes.
3. Conclude locally: \((a_0 \rightarrow a_1 \Rightarrow z_0 \rightarrow z_2) \Rightarrow \text{activation (\texttt{+}) \& threshold = 1.}\)
4. Iterate

\{b = 1\} \Rightarrow \sim
\{b = 0\} \Rightarrow 1+$
Inferring the Interaction Graph

[CMSB12]

→ **Exhaustive search in all possible configurations**

1. Pick one regulator $[a]$, and choose an active process for all the others $[b_0]$.
2. Change the active process of this regulator $[a_0, a_1]$ and watch the **focal processes**.
3. Conclude locally: $(a_0 \uparrow a_1 \Rightarrow z_0 \uparrow z_2) \Rightarrow$ activation $(+)$ & threshold $= 1$.
4. Iterate and conclude globally.
→ Exhaustive search in all possible configurations

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
2. Change the active process of this regulator \([a_0, a_1]\) and watch the focal processes.
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Problematic cases:
→ No focal processes (cycle)
→ Opposite influences (++) & (––) \} \Rightarrow \text{Unsigned edge}
Inferring BRNs from PH models

Translating a Process Hitting into a BRN

Parametrization Inference

Inferring Parameters

[PMR10-TCSB]

Inconclusive cases:

– Behavior cannot be represented as a BRN
– Lack of cooperation (no focal processes)

2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:

– Biological constraints
– The dynamics of the Process Hitting

\[
\begin{array}{cccc}
\omega & k_z, \omega \\
\hline
a & b \\
- & + \\
- & - \\
+ & + \\
+ & - \\
\end{array}
\]
Inferring BRNs from PH models

1. For each configuration of resources \( [\omega = \{a^+, b^-\}] \)

\[
\begin{array}{c|cc}
\omega & a & b \\
\hline
- & + & + \\
+ & + & - \\
\end{array}
\]

Parametrization Inference

Inferring Parameters

\[ [\text{PMR10-TCSB}] \]
1. For each configuration of resources find the focal processes.

[\omega = \{a^+, b^-, a^-, b^+\}]

\begin{align*}
\begin{array}{c|cc}
\omega & a & b \\
\hline
- & + & - \\
+ & - & + \\
+ & - & + \\
\end{array}
\end{align*}
Inferring Parameters

[PMR10-TCSB]

\[
\begin{array}{c|c|c}
\omega & a & b \\
\hline
- & + & \ \ \\
- & - & \ \ \\
+ & + & \ \ \\
+ & - & 1 \\
\end{array}
\]

1. For each configuration of resources \( \omega = \{a^+, b^-\} \) find the \textbf{focal processes}. If possible, conclude. \( k_z, \{a^+, b^-\} = 1 \)
Inferring Parameters

1. For each configuration of resources \([\omega = \{a^+, b^-\}]\) find the focal processes. If possible, conclude. \([k_z, \{a^+, b^-\} = 1]\)

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1. For each configuration of resources \( \omega = \{a^+, b^-\} \) find the focal processes. If possible, conclude. \( k_z,\{a^+, b^-\} = 1 \)

Inconclusive cases:
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2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:
  - Biological constraints
  - The dynamics of the Process Hitting

\[
\begin{array}{ccc}
\omega & & k_z,\omega \\
\hline
a & b & \\
- & + & ? \\
- & - & 0 \\
+ & + & 2 \\
+ & - & ? \\
\end{array}
\]

\[
[k_z,\{a^+, b^-\} \in \{0; 1; 2\}; k_z,\{a^-, b^+\} \in \{0; 1; 2\}]
\]
Implementation

**Workflow:**

- Read and translate the models with **OCaml**
  - Uses the existing free library **Pint**
  - Documentation + examples: [http://processhitting.wordpress.com/](http://processhitting.wordpress.com/)

- Express the problem in **ASP** (logic programming)
  - Solve with **Clingo** (**Gringo** + **Clasp**)
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<th>Parameters inference</th>
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<td><strong>Name</strong></td>
<td>S+CS</td>
<td>P</td>
</tr>
<tr>
<td>[EGFR20]</td>
<td>20+22</td>
<td>152</td>
</tr>
<tr>
<td>[TCRSIG40]</td>
<td>40+14</td>
<td>156</td>
</tr>
<tr>
<td>[TCRSIG94]</td>
<td>94+39</td>
<td>448</td>
</tr>
<tr>
<td>[EGFR104]</td>
<td>104+89</td>
<td>748</td>
</tr>
</tbody>
</table>

S = Sorts  CS = Cooperative sorts  P = Processes  A = Actions

[EGFR20]: Epidermal Growth Factor Receptor, by Özgür Sahin et al.
[EGFR104]: Epidermal Growth Factor Receptor, by Regina Samaga et al.
[TCRSIG40]: T-Cell Receptor Signaling, by Steffen Klamt et al.
[TCRSIG94]: T-Cell Receptor Signaling, by Julio Saez-Rodriguez et al.
Summary

1. Inference of the **complete Interaction Graph**
2. Inference of the **possibly partial Parametrization**
3. Enumerate all full & **admissible Parametrizations**
   → Exhaustive approaches

**Complexity:** linear in the number of genes, exponential in the number of regulators of one gene
Summary

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Conclusion

Existing translation: René Thomas ⇝ Process Hitting
New translation: Process Hitting ⇝ René Thomas

→ **New formal link** between the two models
→ **More visibility** to the Process Hitting
A multi-team topic

**Inoue Laboratory** (NII, Sokendai): Constraint Programming, Systems Biology

**MeForBio** (IRCCyN, ÉCN): Formal Methods for Bioinformatics

**AMIB** (LIX, Polytechnique): Algorithms and Models for Integrative Biology

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Olivier ROUX
Professor & team leader

Morgan MAGNIN
Associate professor

Maxime FOLSCHETTE
2nd year PhD student
Bibliography


Thank you